

### REMARKS

Claims 1, 2, and 5-8 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

1. Applicants note with appreciation that the amendments put forth on October 7, 2004 have been entered in full. Applicants additionally note that the finality of the previous Office Action has been withdrawn.

2. Claims 1, 2, and 5-8 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over US Patent No. 5844079 (Ingham et al.) in view of US Patent No. 6468978 (Esswein et al.). Applicants traverse this rejection.

The Office Action states that “Ingham et al. does teach that the 19 kDa N-terminal fragment becomes active at a concentration of about 5 to 50 pM (~100 to 1000 pg/mL) (See, Office Action, page 3). The Office Action additionally states that “Esswein et al. teach that dipalmitoylated hedgehog proteins exhibit much higher biological activity than non-modified hedgehog proteins.” (See, Office action, page 3). Given the teachings of these two references, the Office Action contends that it would have been obvious to one of skill in the art to select dipalmitoylated hedgehog to modulate chondrocytes, and further that it would have been a matter of routine experimentation to optimize the concentration of dipalmitoylated hedgehog in the range in which the N-terminal fragment becomes active (~100 to 1000 pg/mL).

Regardless of whether Applicants agree that it would have been obvious to one of skill in the art to select dipalmitoylated hedgehog for use in the presently claimed methods, Applicants contend that the combination of references cited by the Examiner in fact teaches away from the presently claimed methods. Accordingly, the combined teachings of Ingham et al. and Esswein et al. fail to undermine the patentability of the presently claimed invention.

The pending claims are directed to methods of making a cartilaginous prosthesis using at least 500 ng/mL of dipalmitoylated hedgehog. This concentration of hedgehog polypeptide is approximately 2-3 orders of magnitude greater than the concentration at which the 19 kDa N-terminal fragment becomes active, as taught by Ingham et al. Not only do the teachings of

Esswein et al. fail to specifically direct one of skill in the art to select a concentration of hedgehog protein greater than that taught by Ingham et al., but in fact, the teachings of Esswein et al. likely direct one of skill in the art to use a decreased concentration of hedgehog. As noted by the Examiner, "Esswein et al. teach that dipalmitoylated hedgehog proteins exhibit much higher biological activity than non-modified hedgehog proteins." (See, Office action, page 3). In light of the greater biological activity of dipalmitoylated hedgehog, one of skill in the art would not have been motivated to use the protein at concentrations 2-3 orders of magnitude greater than the concentration range that Ingham et al. teaches as the range in which the protein becomes active.

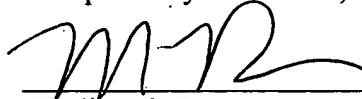
In contrast to the teachings of Ingham et al. and Esswein et al., the present application specifically directs one of skill in the art to select an optimal concentration of hedgehog protein that is 2-3 orders of magnitude greater than that taught by the cited references. Applicants direct the Examiner's attention to, for example, page 9, lines 12-19 which teaches that an optimal concentration of hedgehog protein for use in the presently claimed methods is at least 500 ng/mL. This optimal concentration was neither taught nor suggested by the combined teachings of Ingham et al. and Esswein et al.

Applicants contend that the combined teachings of Ingham et al. and Esswein et al. fail to render the claimed invention obvious. Reconsideration and withdrawal of this rejection is respectfully requested.

**CONCLUSION**

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945, under Order No. CIBT-P01-099.**

Respectfully Submitted,



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